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SPECIAL REPORT

Stress and cardiovascular risk burden after the pandemic: current status and future prospects

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ABSTRACT

Introduction: The recent COVID-19 pandemic has induced an increase in anxiety, stress, and depression in the world population, prompting a reevaluation of these well-known risk factors on cardiovascular burden.

Areas covered: This short report analyzes the impact of the pandemic on stress and depression, highlighting how the phenomenon has particularly affected women and highlights the strategies that can be undertaken after the pandemic to reduce stress and depression. We have analyzed the pandemic because it has completely changed the scenario of cardiovascular risk factors with an important increase in socio-economic stressors

Expert opinion: It is still difficult to assess the damage produced on cardiovascular risk just as it is almost impossible to predict how the overwhelming and important increase in Long-Covid Syndromes will impact the population. Strong action is needed to support critical situations and to implement social campaigns aimed at restoring healthy lifestyles. Physical activity can be an easy and inexpensive tool to help cope with stress and depression.

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Anxiety; cardiovascular disease; depression; gender; lifestyle; stress

1. Introduction

Stress and depression have long been well-known cardiovascular risk factors [1–3]. Their action on blood vessels and the heart has been extensively studied in the past. However, two recent phenomena have brought attention to these risk factors: the identification of the different action of risk factors in the two sexes due to increase attention to gender medicine and the advent of the COVID-19 pandemic which has significantly increased the incidence of depression and stress in the population [4].

Putting the effects of these two phenomena together, it is evident that it is mandatory to reevaluate the role that stress and depression have on the development of atherosclerosis and cardiovascular events.

The mechanisms by which stress and depression act on vessels and on atherosclerosis are partially known. Stress and depression act on endothelial dysfunction through a generalized increase in adrenergic tone which determines a reduction in the vasodilating action of nitric oxide and induces the secretion of pro-inflammatory cytokines. Stress, depression, and anxiety are associated with inflammation and depression of the immune system [5,6]. Stress-induced pathophysiological changes that increase the CV risk burden are summarized in Table 1.

The response to stressful events is generally regarded as the body's reactions to counteract or compensate for stress [7,8].

Physical and psychological stress act through the same pathways and are mainly mediated by the co-activity of the autonomic nervous system (ANS) and the hypothalamus–pituitary–adrenal cortex (HPA) axis [9]. Although the reactivity of both systems is highly specific for the stressor, the results of the former are achieved through several pathways (e.g. ANS system, dopaminergic system) while the results of the second are modified by inputs from cerebral regions [9,10]. The "major players" are epinephrine/norepinephrine (ANS) and cortisol (HPA).

Mental stress also acts on the endothelium, both directly and through oxidative stress and the release of powerful vasoconstrictors, such as endothelin and angiotensin II [11].

Moreover, the reduction of parasympathetic nervous activity induced by mental stress leads to an increased release of proinflammatory cytokines, supported by an important difference between mental stress and physical related stress, where in the latter there is an increase in the parasympathetic nervous discharge [11].

Gender differences in brain activation, autonomic nervous system, cortisol secretion, endothelial dysfunction, inflammatory and immune response have been reported [5]. Some studies reported that the amygdala is an important central nervous system structure in gender-specific CVD events [5]. A neuroimaging study found that the presence of preclinical carotid atherosclerosis correlated with increased reactivity of the amygdala [12].

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Article highlights

- The recent COVID-19 pandemic has induced several socio-economic stressors in the world population,
- Pandemic completely changed the scenario of cardiovascular risk factors with an increase in anxiety, stress, and depression
- Long-Covid Syndromes is now developing and will impact the health of population
- Healthy lifestyle could help to manage stress and anxiety
- Physical activity can be an easy and inexpensive tool to help cope with stress and depression
- Action to recovered healthy lifestyle is needed

Table 1. Stress-induced pathophysiological changes that increase the CV risk burden.

1. Atherosclerotic plaque activation leading to cardiac ischemia
2. Vasoconstriction and increase blood pressure
3. Increase atrioventricular conduction velocity
4. Change in the balance between sympathetic and parasympathetic system
5. Inflammatory systemic status
6. Endothelial dysfunction
7. Depression of immune system
8. Platelet and coagulation activation
9. Increase blood viscosity

Depression is twice as common in women than in men, and this fork begins in mid-puberty and continues over a lifetime [13–15]. Depression is associated with the development of CVD and women are more likely to develop depression-related CV disease [16,17].

Specifically, patients with depressive disorders are more prone to develop acute myocardial infarction, or stroke [18–20]. The INTERHEART study found that mental stress was associated with a greater than twofold increased risk for myocardial infarction even after controlling for CVD risk factors; this effect persisted after stratifying by sex, prior CVD, socioeconomic status, lifestyle factors, and geographic region [21].

In a previous study, we also found that stress was associated with an increased risk of developing paroxysmal atrial fibrillation [22].

Moreover, stress has been linked to stress-induced cardiomyopathy, a transient systolic and diastolic left ventricular dysfunction with wall-motion abnormalities considered an acute heart failure syndrome, the Takotsubo syndrome [23]. Most patients affected by Takotsubo syndrome are women (80–90%), mainly postmenopausal women. In many cases (14–70%) a stressor, emotional or physical are preceded the development of syndrome [23].

Similarly, anxiety, a risk factor for CVD, is more frequent in women than in men throughout life, with a male/female ratio of 1:1.7, and is related to cardiac events in patients with coronary artery disease [24,25].

2. Stress and pandemic

During the pandemic, various social and economic factors led to increased stress in general population and specifically in women. The factors mainly related to women include the role of caring for children during distance learning, caring for the elderly in the family who have been hit hardest by COVID-19, and the consequent reduction in outside work with a subsequent increase in layoffs and economic damage. To all this we must add the fear of getting sick and infecting the family and the impossibility, if got ill, to take care of the most frails relatives [26–28].

Moreover, women experienced pandemic-related stressors specific to reproductive apparatus and stages, i.e. pregnancy, miscarriage, fertility, pregnancy-related disease, postpartum depression, and partner violence [29].

Western health-care systems are focused on the concept of patient-centered care, and during the pandemic changed from patient-centered to community-centered care [30].

This change contributed to increase anxiety and stress in women who have concerns about their health. Furthermore, a spread of stigma was observed as in previous cases of epidemics [31–34].

Media influence can lead to associative stigma that extends to an entire country or city perceived to be at high risk of COVID-19 disease. Continued information on the spread and severity of COVID-19 and conspiracy theories that increase levels of anxiety in people.

The World Health Organization (WHO) defines this flow of (dis)information as "infodemic," This (dis)information has spread in parallel with the escalation of COVID-19, amplified by social media, such as Facebook, Twitter, and Instagram and information channels [35,36].

To combat all these stressors, which in many cases acted simultaneously or in rapid succession, the responses of individuals were varied.

The use of antidepressant drugs was increased during COVID-19 outbreak. A study carried out in the United States found that the prevalence of depression among adults increased threefold during the COVID-19 pandemic compared with the pre-pandemic period [37,38]. Similarly, increased symptoms of depression during the COVID-19 pandemic have also been reported in the UK [39].

A report from Express Scripts, a benefits management program for US-based pharmacies, reported that the number of prescriptions filled per week for anti-anxiety, antidepressant, and anti-insomnia medications increased 21% between February 16 and 15 March 2020 with a peak in the week ending 15 March 2020 when WHO declared the COVID-19 pandemic [40].

The biggest increase in prescriptions was for anxiolytic drugs, which rose 34.1% from mid-February to mid-March, including a weekly peak of nearly 18% during the week ending March 15. Antidepressants and sleep disorders increased by 18.6% and 14.8%, respectively, from February 16 to 15 March 2020 [40]. A similar scenario has been observed in some European countries [41]. Krupa and coworkers found that in Poland the monthly consumption of antidepressants and antianxiety medication between January 2018 and October 2021 increased from almost 40 million doses to almost 60 million. A peak in purchases was recorded in March 2020 with the onset of pandemic in Poland, followed by slightly lower sales over the next 6 months [41]. A similar observation was reported in U.K. were a peak number of antidepressant drugs were dispensed in March 2020 when COVID-19 was officially declared as a pandemic by the World Health

Organization [37]. The overall consumption of anti-depressant drugs was higher throughout the pandemic (January 2020 to September 2020) compared to the consumption in similar months during 2019, except for May and August [37].

It will be interesting to consider whether these prescriptions will remain high even after the pandemic and if the trend will change. Further long-term evaluations will be useful to understand the impact that the pandemic has had on the mental and consequently also physical health of the subjects.

Some subjects counteracted stress and depression with non-pharmacological actions that include a change in lifestyle. During pandemic some subjects switch to an unhealthy diet, rich in fats and sugars and increase the amount of food introduced as highlighted by the sales and consumption data of food [15,42–45].

Eating behaviors are known to differ by sex. In, two population-based telephone interview surveys of adults related to binge eating disorder estimated the point prevalence as 3.3% among women and 0.8% among men [46–48].

As shown by several studies performed during pandemic, women and young people were more likely to 'eating for cope' [49,50].

A very recent analysis showed that young female adults in the Chinese mainland presented higher disordered eating symptoms and were more engaged in online media and weight and fitness management app use than males. Authors concluded that online media exposure and weight and fitness management app use play a crucial role in the generation of disordered eating symptoms in Chinese mainland young adults, especially in females [51].

A study carried out in the United Kingdom, where the stress related to the COVID-19 pandemic was associated with the greater drive for thinness in women suggested that the change in routine caused by the pandemic led women to feel dissatisfied with their bodies and increased restrictive eating and unhealthy weight management practices [52].

Interestingly, some authors reported that the decrease in vegetable consumption was associated with a lower emotional eating score. The authors explained the findings by invoking the Compensatory Health Beliefs, a mechanism by which individuals tend to engage in healthy behavior (i.e. increasing vegetable consumption) to compensate for or counteract unhealthy behavior (i.e. stress, worse sleep, increased amount of food consumed or consumption of sweets and fast food) [53].

Some individuals have increased alcohol and smoking consumption [54]. 'Drinking for cope' was a response characterized by an increase in alcohol consumption to counteract the effects of stress. During pandemic, self-reported increases in alcohol use were observed, with data from cross-sectional studies ranging from 14% to 60% [55,56]. In addition, it is important to understand the correlations of 'drinking to cope,' because it can increase the risk of developing alcohol-related problems in the long term [55,57].

During pandemic, due to restriction induced by Government to contain the outbreak of virus, there was also a reduction in physical and social activity. Moreover, the role of other risk factors such as sedentary lifestyle emerged overwhelmingly [58]. Pandemic increase people sitting time and screen time [52,59–61]. This led to weight gain and increased depression, stress, and insomnia [50,61]. In addition, exposure to screens late at night has a negative impact on sleep–wake rhythms [62].

3. Stress and post-covid

The negative health habits that people developed during the pandemic could persist for a long time. To these must be added: the delays accumulated in the pre-screening visits and the persistence of a widespread fear that the pandemic could recur increasing stress in the population.

Practical recommendations for reducing stress are: resume social contact; engage in sport and relaxing activities; ask for psychological support in the case of persisting signs of anxiety or sleep disorders.

Few data are available on the impact of relaxing activities on cardiovascular risk burden.

Yoga is also included among the activities identified as relaxing, however there is little evidence that yoga acts on cardiovascular risk. A review of yoga's effect on stress reported that in 25/35 trials a yoga intervention significantly reduced stress. However, there are several limitations: for example, most studies include only small samples and do not have a control group, randomized studies are lacking and, above all, there are no validated studies on objectively measurable changes in biomarkers. The word yoga, meaning 'union', is a mind-body-spirit practice that can include meditation, relaxation, breath awareness, and postures. The most likely mechanism is an action on the adrenergic system, and an improve psychological and physical well-being [63,64].

The report of WHO in the first year of the COVID-19 pandemic showed that global prevalence of anxiety and depression increased by a massive 25%, and in the WHO guideline 'Stay physically active during self-quarantine' some meditation and relaxation technique has been suggested [65,66].

Unlike relaxing activities, physical activity has been shown in several studies to reduce stress [67,68].

Regular exercise can lead to adaptations that reduced sensitivity to non-exercise stressors such as psychosocial factors. A strong body of evidence points to the buffering effects of stress from regular exercise (through both the autonomic and hypothalamic systems) [69–72].

Stress responses are generally thought of as the body's reactions to accommodate or compensate for stress. This reaction has previously been described as an activation of the sympathetic-adrenal system (SAM) and the hypothalamus-pituitary-adrenal (HPA) axis. Interestingly, the same response occurs during both exercise and psychological distress (PS). However, the HPA axis response observed during exercise is delayed compared to that induced by psychological stress and indicates the involvement of different emotional neurobiological and cognitive mechanisms [67].

Previous reports have shown the relationship between physical stress and activation of the HPA axis, which deals with the influence of physical activity on stress hormone levels. In addition, higher levels of physical activity are associated with lower HPA axis reactivity at stressor. As a result, physical activity has beneficial effects on both physical and mental health, offering protection against the harmful consequences of chronic stress and stress-related diseases, such as cardiovascular disease and depression [73,74].

A recent longitudinal study evaluated the hypothesis that physical fitness is a predictor of mental health and focused on the stress resilience of modern life as an outcome. Muscular and self-perceived fitness were positively associated with stress resilience, indicated as low symptomatic stressor reactivity over several months [75].

Physical fitness has been shown to provide a more resilient immune defense and greater protection from stress. A reduction in pro-inflammatory cytokine levels (TNF-a and IL-6)

was reported in patients with coronary heart disease after aerobic training and lower IL-6 concentrations were seen in individuals who reported higher physical activity levels [76,77].

Physical activity is a good tool for fighting obesity and reducing associated inflammation. In particular, visceral obesity and sarcopenic obesity led to an increase in cardiovascular risk [78].

Sarcopenic obesity is characterized by the coexistence of excess adiposity and reduced muscle mass/function, a condition increasingly recognized for its clinical and functional characteristics which negatively affect clinical outcomes. Obesity and sarcopenia can therefore synergistically reinforce each other with a vicious cycle of fat gain and muscle loss through reduced mobility and disability [78].

Effective prevention and treatment strategies for sarcopenic obesity are urgently needed. The most effective action is constant and repeated physical exercise [79].

This indication is included in the CV disease prevention guidelines; however, it is poorly applied in real life.

The indications of the WHO in the strategic plan for the prevention of non-communicable diseases are extremely clear in indicating daily physical activity [80]. How can we explain the poor application of these? A determining factor is the low importance that the subject attributes to non-pharmacological therapies. And the difficulty of obtaining results in a short time. In reality, physical activity determines a reduction of the systemic inflammatory state in a short time but this aspect is hardly perceived also due to the lack of objective and rapid biomarkers that measure it.

Moreover, it is not easy to evaluate the effects of physical activity and relaxation against stress for several reasons. First, stress is a ubiquitous aspect of the human experience, ranging from benign everyday stress to chronic stress. Chronic stress can lead to constant chronic inflammation and advanced cellular aging. In addition to that, the mechanisms by which excessive stress exposure increases CVD risk burden are multifactorial and have not been fully elucidated. Finally, both the magnitude of the stress and the physiological effects of the stressors are likely to be dependent on resilience and coping strategies and change throughout life. Personalized strategies need to be developed in order to obtain results.

4. Expert opinion

An important factor that hinders the return to normality after pandemic, and a good management of anxiety, stress, and depression is the post-Covid 19 syndrome which, due to its duration, can evolve into Long Covid syndrome.

After inpatient treatment for COVID-19, middle-aged women have been reported to have a higher chance of developing a variety of devastating symptoms such as fatigue, muscle pain, shortness of breath, anxiety, depression, and 'brain fog' due to persistent inflammation [4]. However, long COVID is not limited to patients with severe clinical manifestations. In many subjects affected by 'mild' COVID-19, symptoms include persistent fatigue and dyspnea, palpitations, and headache. Moreover, a number of subjects also develop cognitive problems, including poor memory and short concentration. The symptoms of the long Covid favor a sedentary life which in turn favors unhealthy habits such as an increase in snacks and foods rich in sugar, eating in front of the screen that leads to eating more. This is in addition to the lack of physical activity caused by limiting symptoms such as fatigue, muscle pain and dyspnea. It is very difficult to promote a return to healthy life in people with long Covid. The prolonged effects of Covid also on the brain level increase the risk of depression and a vicious circle is created which together with the unhealthy lifestyle leads the subject to social isolation.

Physical activity can be an easy and inexpensive tool to help cope with stress and depression.

There is a strong body of evidence supporting the anxiolytic effects of acute and regular physical activity in adults and older adults [81,82]

Some randomized controlled studies investigating the effects of aerobic exercise on stress have employed moderate continuous aerobic exercise at volumes comparable to that suggested by the Federal Physical Activity guidelines and therefore little is known about the potential graded effects of higher intensities of aerobic exercise on stress [81,82].

A strong action is needed to counteract the increase in stress and depression in the population. It is mandatory to implement psychological support in critical situations and to implement social campaigns aimed at restoring healthy lifestyles.

Personalized actions must be aimed at subjects with moderate/high cardiovascular risk and must be built on the analysis of individual risk and the subject's resilience. Finally, a different approach must be used in the two sexes due to the different pathophysiological responses in the man and the woman [83,84].

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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